

TENT COOPERATION TRE. Y

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

BAYER AKTIENGESELLSCHAFT
D-51386 Leverkusen
ALLEMAGNE

Date of mailing (day/month/year) 11 January 2001 (11.01.01)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference SJW/44111	
International application No. PCT/GB99/02267	International filing date (day/month/year) 14 July 1999 (14.07.99)

1. The following indications appeared on record concerning:

☒ the applicant
 ☐ the inventor
 ☐ the agent
 ☐ the common representative

Name and Address

 THE HONG KONG UNIVERSITY OF
SCIENCE & TECHNOLOGY
Clear Water Bay
Kowloon
Hong Kong
China

State of Nationality

CN

State of Residence

CN

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person
 ☐ the name
 ☐ the address
 ☐ the nationality
 ☐ the residence

Name and Address

 BAYER AKTIENGESELLSCHAFT
D-51386 Leverkusen
Germany

State of Nationality

DE

State of Residence

DE

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
 ☐ the designated Offices concerned
☐ the International Searching Authority
 ☒ the elected Offices concerned
☐ the International Preliminary Examining Authority
 ☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Elisabeth KÖNIG Telephone No.: (41-22) 338.83.38
---	---

TENT COOPERATION TRE; Y

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

WALLACE, Sheila, Jane
Lloyd Wise Tregear & Co.
Commonwealth House
1-19 New Oxford Street
London WC1A 1LW
ROYAUME-UNI

Date of mailing (day/month/year) 21 February 2000 (21.02.00)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference SJW/44111	
International application No. PCT/GB99/02267	International filing date (day/month/year) 14 July 1999 (14.07.99)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address	State of Nationality DE	State of Residence DE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☒ the name ☒ the address ☒ the nationality ☒ the residence

Name and Address GREIF, Gisela Marienhöhe 15 D-53424 Remagen-Rolandswerth Germany	State of Nationality DE	State of Residence DE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

Additional applicant/inventor for the purposes of the United States of America only. A power of attorney executed by the new applicant is required.

4. A copy of this notification has been sent to:

<input checked="" type="checkbox"/> the receiving Office	<input checked="" type="checkbox"/> the designated Offices concerned
<input checked="" type="checkbox"/> the International Searching Authority	<input type="checkbox"/> the elected Offices concerned
<input type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Dominique DELMAS Telephone No.: (41-22) 338.83.38
---	--

TENT COOPERATION TRE, Y

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09/10/99
5F00

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

BAYER AKTIENGESELLSCHAFT
D-51368 Leverkusen
ALLEMAGNE

Date of mailing (day/month/year) 02 February 2001 (02.02.01)	
Applicant's or agent's file reference SJW/44111	IMPORTANT NOTIFICATION
International application No. PCT/GB99/02267	International filing date (day/month/year) 14 July 1999 (14.07.99)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address BAYER AKTIENGESELLSCHAFT D-51386 Leverkusen Germany	State of Nationality DE	State of Residence DE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address BAYER AKTIENGESELLSCHAFT D-51368 Leverkusen Germany	State of Nationality DE	State of Residence DE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office ☐ the designated Offices concerned
☐ the International Searching Authority ☒ the elected Offices concerned
☐ the International Preliminary Examining Authority ☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Dominique DELMAS
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

BAYER AKTIENGESELLSCHAFT
D-51368 Leverkusen
ALLEMAGNE

Date of mailing (day/month/year) 02 February 2001 (02.02.01)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference SJW/44111	
International application No. PCT/GB99/02267	International filing date (day/month/year) 14 July 1999 (14.07.99)

1. The following indications appeared on record concerning:

☐ the applicant

 ☐ the inventor

 ☐ the agent

 ☒ the common representative

Name and Address

BAYER AKTIENGESELLSCHAFT
D-51386 Leverkusen
Germany

State of Nationality

State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person

 ☐ the name

 ☒ the address

 ☐ the nationality

 ☐ the residence

Name and Address

BAYER AKTIENGESELLSCHAFT
D-51368 Leverkusen
Germany

State of Nationality

State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned
<input type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Dominique DELMAS

Telephone No.: (41-22) 338.83.38

TENT COOPERATION TRE. Y

PCT

5000

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

BAYER AKTIENGESELLSCHAFT
D-51386 Leverkusen
ALLEMAGNE

Date of mailing (day/month/year) 11 January 2001 (11.01.01)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference SJW/44111	
International application No. PCT/GB99/02267	International filing date (day/month/year) 14 July 1999 (14.07.99)

1. The following indications appeared on record concerning:

☐ the applicant

 ☐ the inventor

 ☒ the agent

 ☐ the common representative

Name and Address

WALLACE, Sheila, Jane
Lloyd Wise, Tregear & Co.
Commonwealth House
1-19 New Oxford Street
London WC1A 1LW
United Kingdom

State of Nationality

State of Residence

Telephone No.

+44 (0)20 7571 6200

Facsimile No.

+44 (0)20 7571 6250

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person

 ☐ the name

 ☐ the address

 ☐ the nationality

 ☐ the residence

Name and Address

BAYER AKTIENGESELLSCHAFT
D-51386 Leverkusen
Germany

State of Nationality

State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

The agent indicated in Box No. 1 has resigned from representation. The person indicated in Box No. 2 has been registered as common representative.

4. A copy of this notification has been sent to:

<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned
<input type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Elisabeth KÖNIG Telephone No.: (41-22) 338.83.38
--	---

TENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C. 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 06 March 2000 (06.03.00)	
International application No. PCT/GB99/02267	Applicant's or agent's file reference SJW/44111
International filing date (day/month/year) 14 July 1999 (14.07.99)	Priority date (day/month/year) 14 July 1998 (14.07.98)
Applicant HAYNES, Richard, Kingston et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

11 February 2000 (11.02.00)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Lazar Joseph Panakal

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

CORRECTED

PCT
VERSIONNOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

WALLACE, Sheila, Jane
Lloyd Wise Tregear & Co.
Commonwealth House
1-19 New Oxford Street
London WC1A 1LW
ROYAUME-UNI

Date of mailing (day/month/year) 05 April 2000 (05.04.00)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference SJW/44111	
International application No. PCT/GB99/02267	
	International filing date (day/month/year) 14 July 1999 (14.07.99)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address

State of Nationality

State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address

GREIF, Gisela
Marienhöhe 15
D-53424 Remagen-Rolandswerth
Germany

State of Nationality

DE

State of Residence

DE

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

Addition of inventor and applicant for US only. Power of attorney executed by the new applicant is required.

4. A copy of this notification has been sent to:

☒ the receiving Office ☒ the designated Offices concerned
☒ the International Searching Authority ☐ the elected Offices concerned
☐ the International Preliminary Examining Authority ☐ other:
The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Anman QIU

Facsimile No.: (41-22) 740.14.35

Telephone No.: (41-22) 338.83.38

CORRECTED TENT COOPERATION TRE. VERSION

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

WALLACE, Sheila, Jane
Lloyd Wise Tregear & Co.
Commonwealth House
1-19 New Oxford Street
London WC1A 1LW
ROYAUME-UNI

Date of mailing (day/month/year) 05 April 2000 (05.04.00)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference SJW/44111	
International application No. PCT/GB99/02267	International filing date (day/month/year) 14 July 1999 (14.07.99)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address VOERSTE, Arnd Salierring 33 D-50677 Köln Germany	State of Nationality DE	State of Residence DE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

Addition of inventor and applicant for US only. Power of attorney executed by the new applicant is required.

4. A copy of this notification has been sent to:

☒ the receiving Office ☒ the designated Offices concerned
☒ the International Searching Authority ☐ the elected Offices concerned
☐ the International Preliminary Examining Authority ☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Anman QIU Telephone No.: (41-22) 338.83.38
---	---

CORRECTED

INTERNATIONAL COOPERATION TREATY

VERSION

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

WALLACE, Sheila, Jane
Lloyd Wise Tregear & Co.
Commonwealth House
1-19 New Oxford Street
London WC1A 1LW
ROYAUME-UNI

Date of mailing (day/month/year) 05 April 2000 (05.04.00)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference SJW/44111	
International application No. PCT/GB99/02267	International filing date (day/month/year) 14 July 1999 (14.07.99)

1. The following indications appeared on record concerning:		
<input checked="" type="checkbox"/> the applicant	<input checked="" type="checkbox"/> the inventor	<input type="checkbox"/> the agent <input type="checkbox"/> the common representative
Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	
2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:		
<input checked="" type="checkbox"/> the person	<input type="checkbox"/> the name	<input type="checkbox"/> the address <input type="checkbox"/> the nationality <input type="checkbox"/> the residence
Name and Address SCHMUCK, Gabriele Am Ringhofen 17 D-42327 Wuppertal Germany	State of Nationality DE	State of Residence DE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	
3. Further observations, if necessary: Addition of inventor and applicant for US only. Power of attorney executed by the new applicant is required.		
4. A copy of this notification has been sent to:		
<input checked="" type="checkbox"/> the receiving Office	<input checked="" type="checkbox"/> the designated Offices concerned	
<input checked="" type="checkbox"/> the International Searching Authority	<input type="checkbox"/> the elected Offices concerned	
<input type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:	

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Anman QIU Telephone No.: (41-22) 338.83.38
---	---

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference SJW/44111	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/GB 99/ 02267	International filing date (day/month/year) 14/07/1999	(Earliest) Priority Date (day/month/year) 14/07/1998
Applicant THE HONG KONG UNIVERSITY OF SCIENCE & TECHNOLOGY		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

ANTIPARASITIC ARTEMISININ DERIVATIVES (ENDOPEROXIDES)

5. With regard to the **abstract**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

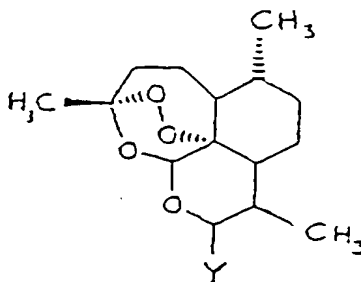
☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

//////
☐ None of the figures.

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

This invention relates to the use of certain C-10 substituted derivatives of artemisinin of the general formula I



in the treatment and/or prophylaxis of diseases caused by infection with a parasite, certain novel C-10 substituted derivatives of artemisinin, processes for their preparation and pharmaceutical compositions containing such C-10 substituted derivatives. The compounds are particularly effective in the treatment of malaria, neosporosis and coccidiosis.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 99/02267

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D493/18 A61K31/335 A61K31/35 //((C07D493/18,241:00),
 (C07D493/18,307:00),(C07D493/18,209:00),(C07D493/18,265:00),
 (C07D493/18,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JEFFORD, C.W.: "Peroxidic Antimalarials" ADV.DRUG RES., vol. 29, 1997, pages 271-325, XP002119844 LONDON * see page 320, 2nd par., last sentence * the whole document ---	1-27
X	MESHNICK S R ET AL: "ARTEMISININ AND THE ANTIMALARIAL ENDOPEROXIDES: FROM HERBAL REMEDY TO TARGETED CHEMOTHERAPY" MICROBIOLOGICAL REVIEWS, vol. 60, no. 2, 1 June 1996 (1996-06-01), pages 301-315, XP002052313 * see page 306, right col., last par. * the whole document --- -/--	1-27



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

3 November 1999

Date of mailing of the international search report

30. 11. 99

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Stellmach, J

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/02267

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 26 and 27 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No.

T/GB 99/02267

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	TONMUNPHEAN, S. ET AL.: "Comparative molecular field analysis of artemisinin derivatives: Ab initio versus semiempirical optimized structures " J.COMP.-AIDED MOL.DES., vol. 12, 1998, pages 397-409, XP002120343 AMSTERDAM	1-15, 20
X	* see p.402, fig. 2 * the whole document	16-25
X	LUO ET AL: "The Chemistry, Pharmacology, and Clinical Applications of Qinghaosu (Artemisinin) and Its Derivatives" MEDICINAL RESEARCH REVIEWS, vol. 7, no. 1, 1 January 1987 (1987-01-01), pages 29-57, XP002088809 ISSN: 0198-6325 the whole document	1-27
Y	YONG-HUA Y ET AL: "Artemisinin derivatives with 12-aniline substitution: synthesis and antimalarial activity" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 5, no. 16, 17 August 1995 (1995-08-17), page 1791-1794 XP004135366 ISSN: 0960-894X the whole document	1-27
Y	PU ET AL: "Synthesis and Antimalarial Activities of Several Fluorinated Artemisinin Derivatives" JOURNAL OF MEDICINAL CHEMISTRY, vol. 38, no. 20, 1 January 1995 (1995-01-01), pages 4120-4124, XP002089611 ISSN: 0022-2623 the whole document	1-27
X	JUNG, M. ET AL.: "A Concise Synthesis of Novel Aromatic Analogs of Artemisinin" HETEROCYCLES, vol. 45, no. 6, 1997, pages 1055-1058, XP002120565 SENDAI the whole document	1-27
X	CN 1 122 806 A (SHANGHAI INST OF MATERIA MEDIC) 22 May 1996 (1996-05-22) the whole document	1-27
X	US 5 225 562 A (MCCHESNEY JAMES D ET AL) 6 July 1993 (1993-07-06) the whole document	1-27
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/02267

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 456 149 A (HOECHST AG) 13 November 1991 (1991-11-13) the whole document ---	1-27
X	EP 0 362 730 A (HOECHST AG) 11 April 1990 (1990-04-11) the whole document ---	1-27
Y	WO 93 08195 A (UNIV SYDNEY) 29 April 1993 (1993-04-29) the whole document ---	1-27
P,X	POSNER, G.H.: "Antimalarial peroxides in the quinghaosu (artesimin) and yingzhaosu families" EXP.OPIN.THER.PATENTS, vol. 8, no. 11, November 1998 (1998-11), pages 1487-1493, XP002119814 LONDON the whole document ---	1-15,20
P,X	WO 99 33461 A (HAUSER INC ; UNIV JOHNS HOPKINS (US)) 8 July 1999 (1999-07-08) the whole document -----	1-27

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/02267

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
CN 1122806	A	22-05-1996	NONE	
US 5225562	A	06-07-1993	NONE	
EP 0456149	A	13-11-1991	AU 639095 B AU 7618591 A JP 4225983 A PT 97577 A US 5246930 A	15-07-1993 07-11-1991 14-08-1992 31-01-1992 21-09-1993
EP 0362730	A	11-04-1990	AU 629571 B AU 4242189 A CN 1041595 A JP 2145586 A MX 17808 A NZ 230868 A US 5225427 A	08-10-1992 12-04-1990 25-04-1990 05-06-1990 31-03-1994 26-08-1992 06-07-1993
WO 9308195	A	29-04-1993	AU 659505 B JP 7500325 T	18-05-1995 12-01-1995
WO 9933461	A	08-07-1999	AU 2018499 A	19-07-1999

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

17

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference IP14631/MCF	FOR FURTHER ACTION		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB99/02287	International filing date (day/month/year) 15/07/1999	Priority date (day/month/year) 16/07/1998	
International Patent Classification (IPC) or national classification and IPC A47K7/04			
Applicant BROWNING, Tony			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of **5** sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 16/02/2000	Date of completion of this report 18. 04 2000
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Delzor, F Telephone No. +31 70 340 3507

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB99/02287

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-4 as originally filed

Claims, No.:

1-10 as originally filed

Drawings, sheets:

1/4-4/4 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
☒ claims Nos. 10.

because:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/02287

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 10 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 1-9
	No: Claims
Inventive step (IS)	Yes: Claims 1-9
	No: Claims
Industrial applicability (IA)	Yes: Claims 1-9
	No: Claims

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 10 does not contain any technical features and is only defined with reference to the drawings, contrary to the requirements of Rule 6.2(a) PCT.

Therefore, no examination can be performed on claim 10, which should not have been part of the application.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The difference between the hand cleansing apparatus of the invention and the hand cleansing apparatus disclosed by document DE-A-3604256 is that the hand resting surface defining one side of the gap is convex, which tends to urge the fingers apart. Such a configuration of the resting surface provides a better cleansing between the fingers.

Means forcing fingers apart in order to provide a better access for a cleansing fluid is not known from the state of the art.

Therefore, the subject-matter of independent claim 1 and of dependent claims 2-9 is considered to involve an inventive step (Rule 65(1)(2) PCT).

Re Item VII

Certain defects in the international application

- 1) Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document DE-A-3604256 is not mentioned in the description, nor is this document identified therein.
- 2) Independent claim 1 is not in the two-part form in accordance with Rule 6.3(b) PCT, which in the present case would have been appropriate, with those features known in combination from the prior art (document DE-A-3604256) being placed in the

preamble (Rule 6.3(b)(i) PCT) and with the remaining features being included in the characterising part (Rule 6.3(b)(ii) PCT).

In the present case claim 1 could have read:

"Hand cleansing apparatus comprising means defining a gap to receive human fingers, said means including a surface defining one side of the gap, nozzle on one side of the gap for directing fluid into the gap and means for supplying cleansing fluid to the nozzle, characterised in that said surface is convex for tending to urge said fingers apart when said fingers contact the convex surface.

3) The features of the claims are not provided with reference signs placed in parentheses (Rule 6.2(b) PCT).

PATENT COOPERATION TREATY

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REC'D 17 OCT 2000

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SJW/44111		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) FOR FURTHER ACTION	
International application No. PCT/GB99/02267	International filing date (day/month/year) 14/07/1999	Priority date (day/month/year) 14/07/1998	
International Patent Classification (IPC) or national classification and IPC C07D493/18			
Applicant THE HONG KONG UNIVERSITY OF SCIENCE & TECH. et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 10 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 11/02/2000	Date of completion of this report 13.10.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Stellmach, J Telephone No. +49 89 2399 8279 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB99/02267

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-76 as originally filed

Claims, No.:

1-27 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
☒ claims Nos. 26,27.

because:

- ☒ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB99/02267

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	16-19, 21-27
	No:	Claims	1-15,20
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-27
Industrial applicability (IA)	Yes:	Claims	1-25
	No:	Claims	

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB99/02267

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

SECTION III -----

1. Claims 26 and 27 relate to subject-matter considered by this Authority to be covered by the provisions of **Rule 67.1(iv) PCT**. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (**Article 34(4)(a)(i) PCT**).
2. Under the terms of **Rule 39.1 (iv) PCT**, the International Preliminary Examination Authority is not required to carry out an examination of claims directed to a **method of treatment** of the human or animal body by surgery or therapy. As indicated in the Search Report, the search was carried out and based on the **alleged effects** of the compounds (**Rule 67.1 (iv) PCT**).

SECTION V -----

1. Prior art

Documents (1) - (15), which were all cited in the **Written Opinion** are considered to represent relevant prior art in this **Preliminary Examination Report**; the numbering will be adhered to in the rest of the procedure.

- (1) Adv.Drug Res. 29, 271 (1997)
- (2) Microbiol.Rev. 60, 301 (1996)
- (3) J.Comp.Aid.Mol.Des. 12, 397 (1998)
- (4) Med.Res.Rev. 7, 29 (1987)
- (5) Bioorg.Med.Chem.Lett. 5, 1791 (1995)
- (6) J.Med.Chem. 38, 4120 (1995)
- (7) Heterocycles 45, 1055 (1997)
- (8) CN-A-1122 806

- (9) US-A-52 25 562
- (10) EP-A-0 456 149
- (11) EP-A-0 362 730
- (12) WO-A-93/08 195
- (13) Exp.Opin.Ther.Patents 8, 1487 (1998)
- (14) WO-A-99/33 461
- (15) CN-A-1052 26 73

2. Novelty and unity

2.1 Documents (13) and (14) are only relevant for the purposes of **Rules 33.1 c, 64.3 and 70.10 PCT** (see also part VI, certain documents) and since the priority document is not available are not taken into account for the **Preliminary Examination Report**. If the priority date is not valid for the complete claimed subject-matter, documents (13) and (14) may become relevant prior art in a possible regional / national phase.

2.2 Claims 1 - 15 refer to the (first) use of known *anti-malaria/anti-parasitic artemisinin* derivatives for any further *antiparasitic use* except the known one. Since a **first medical use** is already known for many of the claimed compounds, only a **second medical use** is allowable. At present the requirements of **Article 33 (2) PCT** are not met. Moreover, such **disclaimers/ provisos** are not allowed, since the term *antiparasitic* (active against the malaria parasite) includes the term **anti-malaria**. Accordingly, insofar the claimed use is included in the prior art use (same pharmacological activity), the present application lacks **unity** of invention (**Rule 13 PCT**). At least for the general formula of claim 1 there exists no "**single general inventive concept**", since starting from the viewpoint that all compounds of the general formula of claim 1 are equivalent in so far as a possibly new use is concerned, (thereby conferring **unity** on the claim), the fact that a certain use included in the general use is found not to be inventive then would mean that none of the other - **equivalent** - uses can be **inventive**. If however, the general use (*antiparasitic*) is not to be regarded as **equivalent**, then **lack of unity**

exists (no "**special technical feature**" which defines a contribution of all the claimed inventions (equivalents) considered as a whole make over the prior art. It is stressed there is no basis for the substantiation of **inventive step** by way of **disclaimer**. Since claim 20 refers to the preparation of **known and novel** compounds of claim 1, there are additionally at least two different **novelty** rendering features (the new use and the different reaction parameter) in comparison with the respective closest prior art. The Applicant's attention is drawn to the fact that the requirements of **unity (common technical feature** in order to belong to a common inventive concept, single inventive concept, see **Rule 13 (1) (2) PCT**), again are not met.

2.3 Claims 16 - 19 and 21 - 25 refer to a generic formula of **artemisinin** derivatives (namely formula I of claim 1), from which some 10-aminoaryl derived compounds with the same pharmacological activity are **disclaimed** by a **proviso**, because they are no longer novel (see citations (5) and (9)). However, also the general formula disclosed in citations (3), (7) and (8) **overlap** with that of claim 1 respective claim 16. Accordingly, the subject-matter of claim 16 and its dependant claims lacks **unity of invention** (common technical feature in order to belong to a **common inventive concept**, single inventive concept, see **Rule 13 (1) (2) PCT**). It is noted that the compounds known from citations (3), (5) and (7) - (9) illustrate the same pharmacological activity as those claimed. For the general formula of claim 16 there exists no "**single general inventive concept**", since starting from the viewpoint that all compounds with the general formula of claim 1 are **equivalent** (thereby conferring unity on the claim), the fact that a group of compounds is found not to be **inventive** then means that none of the other - **equivalent** - compounds can be inventive. If however, the compounds are not to be regarded as **equivalent**, then **lack of unity** exists (no "special technical feature" which defines a contribution of all the claimed inventions (equivalents) considered as a whole make over the prior art. It is again stressed there is no basis for the substantiation of **inventive step** by way of **disclaimer**.

2.4 Having regard to the available prior art (1), (2), (4), (6) and (10) - (12) it is noted that the claimed subject-matter of claim 16 and its dependant claims appears to fulfil the requirements of **Article 33 (2) PCT**, since the claimed substituted **artemisinin** derivatives (analogues of known lead compounds) differ from those of the prior art by the definition of the substituent Y in 10-position of the tricyclic endoperoxide.

3. Inventive step

3.1 Assessment of **inventive step** is only possible for **unitary** and **novel** subject-

matter, so that the following opinion is only **provisional**. With regard to the requirement for inventive step (**Article 33 (3) PCT**) of the claimed subject-matter, a document has to be identified which represents the (respective) closest prior art for the claimed compounds. All the cited prior art documents disclose artemisinin derivatives with *anti-parasitic/anti-malaria activity*.

3.2 Starting from the closest prior art (to be decided for unitary and novel subject-matter), the first technical problem underlying the application in suit (**Article 33 (3) PCT, Rule 5.1 (a) (iii) PCT**) can be considered to be the provision of further endo-peroxide (1,2,4-trioxane, artemisinin analogues) derivatives with **unexpected** pharmacological activity. At present it is not possible to decide whether any structural modification is not directly suggested in the cited prior art. However, the skilled person having a basic knowledge of the principles of **structure-activity-relationships** would expect the claimed compounds to illustrate *anti-parasitic activity*. With regard to the possible technical/structural difference to the prior art (to be indicated by the Applicant), the claimed derivatives must be considered as close structural analogues of some mentioned in the prior art. The maintenance of the pharmacological activity is thus to be expected for the skilled person i.e. the skilled person having knowledge of the teaching of the prior art would consider at least some of the claimed derivatives to illustrate *anti-parasitic activity*. For the skilled person starting from the compounds disclosed in particular in (3), (5) and (7) - (9) there is thus a clear **incentive** that the resulting compounds display *anti-parasitic activity*. Having regard to the structural differences (to be described by the Applicant for novelty and unity) vis-a-vis the respective prior art, these modifications lie within the usual skill of the application of **structure-activity-relationships**. The skilled man would have been able to predict that the same pharmacological activity would be retained due to these structural modifications which are already suggested in the prior art for structural similar *antiparasitic* compounds. There is thus a **reasonable expectation of success** to arrive at compounds displaying *anti-parasitic activity*. In this respect the Applicant's attention is drawn to citations (1) and (2) (see the International Search Report), which clearly teach and suggest that other *anti-parasitic* than *anti-malarial activity* is known for artemisinin analogues. This is confirmed by the **reaction mechanism** (alkylation of protein, oxidative activation, interaction with heme, see 'inter alia' citations (1) , (2) and (4)).

3.3 Accordingly, at present the requirements of **Article 33 (3) PCT** are not met. Given the properties to be expected for the claimed compounds (analogues) in comparison with those of the prior art, an inventive step could be recognized if the Appli-

cant could demonstrate that the presently claimed compounds illustrate any **unpredictable** (qualitatively or quantitatively) pharmacological activity. The pharmacological tests performed with some of the claimed compounds (see pages 67 - 77) cannot be taken into account, since the *parasitocidal activity* as such is not surprising and the comparison with **artemisinin** does not reflect the closest possible structural approximation.

3.4 Finally, it is realized that the Applicant is entitled to claim all obvious modifications of what he has described and that alternative variations have to be supported by a certain number of examples. Furthermore, the extent of a "**reasonable generalisation**" only depends upon the question of the relative distance to the prior art compounds. It is stressed that only such compounds can be claimed which are a solution to the above stated problem i.e. which illustrate the alleged unexpected pharmacological activity. Expressions in claim 1 (and the reference claim 16) like "**optionally substituted**" in particular in combination with "**heterocyclic group**" or "**heterocyclalkyl**" are **speculative** in the sense of **Article 33 (3) PCT**, embracing a great variety of structural possibilities not yet explored by the Applicant, the effect of which cannot be foreseen having regard to the problem underlying the present application. Moreover, such definitions create unnecessary **overlap** and **selection** situations. Such expressions - encompass other chemical residues /heterocycles - including any other moiety being known for their *antiparasitic activity*. Furthermore, also the attachment of other biophoric/ pharmacophoric molecules as well as **bioconjugates** are embraced, so that the actual biological activity of e.g. the resulting **hybrid molecules** is unpredictable. Having regard to the problem underlying the present application it cannot be foreseen, whether such molecules are either an obvious solution or a solution to the problem at all. Finally, such **extremely broad** generalisations obviously are in contradiction to the basis of (qualitative) **structure-activity-relationships**.

4. Industrial applicability

4.1 No objection re industrial applicability of claims 1 - 25 arises insofar the claimed compounds would exhibit the alleged unexpected pharmacological properties (**Article 33 (4) PCT**).

4.2 For the assessment of the present claims 26 and 27 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a com-

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/02267

pound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

SECTION VI -----

WO-A-99/33 461	8.7.99	30.12.98	30.12.97
			30.10.98

SECTION VII -----

1. Whereas claims 1 - 15 refer to first medical **use** claims, several other claims are compound claims. With regard to the absolute compound protection, for reasons of clarity the reference should start from compound claims and not from use claims. The requirements of **Article 6 PCT** at present are not met.
2. Since the documents (1) - (15) were not identified in the description and the relevant background art disclosed therein was not briefly discussed, the requirements of **Rule 5.1 (a) (ii) PCT** are not met.
3. The dependent claims are only possible as specific form in conjunction with independent claims of the invention (**Rule 6.4 PCT**).

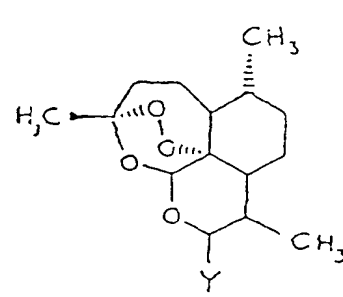
SECTION VIII-----

The Applicant is informed that the breadth of the claims has to be such that it comprises only variants which are able to solve the problem underlying the invention being a prerequisite for the acknowledgement of inventive step (**Article 33 (3) PCT**).

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WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification 7 : C07D 493/18, A61K 31/335, 31/35 // (C07D 493/18, 241:00) (C07D 493/18, 307:00) (C07D 493/18, 209:00) (C07D 493/18, 265:00) (C07D 493/18, 221:00)</p>	A1	<p>(11) International Publication Number: WO 00/04024</p> <p>(43) International Publication Date: 27 January 2000 (27.01.00)</p>
<p>(21) International Application Number: PCT/GB99/02267</p> <p>(22) International Filing Date: 14 July 1999 (14.07.99)</p> <p>(30) Priority Data: 98305596.3 14 July 1998 (14.07.98) EP</p> <p>(71) Applicant (for all designated States except US): THE HONG KONG UNIVERSITY OF SCIENCE & TECHNOLOGY [CN/CN]; Clear Water Bay, Kowloon, Hong Kong (CN).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): HAYNES, Richard, Kingston [AU/CN]; The Hong Kong University of Science & Technology, House 2, 1 University Road, Clear Water Bay, Kowloon, Hong Kong (CN). CHAN, Ho-Wai [GB/CN]; Flat 15, 2/F, Kam Yung House, Kam Fung Court, Ma On Shan, Shatin, New Territories, Hong Kong (CN). LAM, Wai-Lun [GB/CN]; 6/F 100 Shantung Street, Mongkok, Kowloon, Hong Kong (CN). TSANG, Hing-Wo [GB/CN]; 20A To Shek Village, Sha Tin, New Territories, Hong Kong (CN). CHEUNG, Man-Ki [GB/CN]; Flat 4B Block 14, Laguna City, Cha Kwo Ling, Kowloon, Hong Kong (CN).</p>		<p>(74) Agent: WALLACE, Sheila, Jane; Lloyd Wise Tregear & Co., Commonwealth House, 1-19 New Oxford Street, London WC1A 1LW (GB).</p> <p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>
<p>(54) Title: ANTIPARASITIC ARTEMISININ DERIVATIVES (ENDOPEROXIDES)</p> <p>(57) Abstract</p> <p>This invention relates to the use of certain C-10 substituted derivatives of artemisinin of general formula (I) in the treatment and/or prophylaxis of diseases caused by infection with a parasite, certain novel C-10 substituted derivatives of artemisinin, processes for their preparation and pharmaceutical compositions containing such C-10 substituted derivatives. The compounds are particularly effective in the treatment of malaria, neosporosis and coccidiosis.</p> <div style="text-align: right;"><p>(I)</p></div>		

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DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

INTERNATIONAL SEARCH REPORT

Int. l. Application No
PCT/GB 99/02267

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07D493/18 A61K31/335 A61K31/35 //(C07D493/18,241:00), (C07D493/18,307:00), (C07D493/18,209:00), (C07D493/18,265:00), (C07D493/18,221:00)		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the International search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JEFFORD, C.W.: "Peroxidic Antimalarials" ADV. DRUG RES., vol. 29, 1997, pages 271-325, XP002119844 LONDON * see page 320, 2nd par., last sentence * the whole document	1-27
X	MESHNICK S R ET AL: "ARTEMISININ AND THE ANTIMALARIAL ENDOPEROXIDES: FROM HERBAL REMEDY TO TARGETED CHEMOTHERAPY" MICROBIOLOGICAL REVIEWS, vol. 60, no. 2, 1 June 1996 (1996-06-01), pages 301-315, XP002052313 * see page 306, right col., last par. * the whole document	1-27
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<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.		
<input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>*A* document defining the general state of the art which is not considered to be of particular relevance</p> <p>*E* earlier document but published on or after the international filing date</p> <p>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>*O* document referring to an oral disclosure, use, exhibition or other means</p> <p>*P* document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>*Z* document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search <div style="text-align: center; font-weight: bold;">3 November 1999</div>		Date of mailing of the international search report <div style="text-align: center; font-weight: bold;">30. 11. 99</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3016		Authorized officer <div style="text-align: center; font-weight: bold;">Stellmach, J</div>

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	TONMUNPHEAN, S. ET AL.: "Comparative molecular field analysis of artemisinin derivatives: Ab initio versus semiempirical optimized structures " J.COMP.-AIDED MOL.DES., vol. 12, 1998, pages 397-409, XP002120343 AMSTERDAM	1-15, 20
X	* see p.402, fig. 2 * the whole document	16-25
X	LUO ET AL: "The Chemistry, Pharmacology, and Clinical Applications of Qinghaosu (Artemisinin) and Its Derivatives" MEDICINAL RESEARCH REVIEWS, vol. 7, no. 1, 1 January 1987 (1987-01-01), pages 29-57, XP002088809 ISSN: 0198-6325 the whole document	1-27
Y	YONG-HUA Y ET AL: "Artemisinin derivatives with 12-aniline substitution: synthesis and antimalarial activity" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 5, no. 16, 17 August 1995 (1995-08-17), page 1791-1794 XP004135366 ISSN: 0960-894X the whole document	1-27
Y	PU ET AL: "Synthesis and Antimalarial Activities of Several Fluorinated Artemisinin Derivatives" JOURNAL OF MEDICINAL CHEMISTRY, vol. 38, no. 20, 1 January 1995 (1995-01-01), pages 4120-4124, XP002089611 ISSN: 0022-2623 the whole document	1-27
X	JUNG, M. ET AL.: "A Concise Synthesis of Novel Aromatic Analogs of Artemisinin" HETEROCYCLES, vol. 45, no. 6, 1997, pages 1055-1058, XP002120565 SENDAI the whole document	1-27
X	CN 1 122 806 A (SHANGHAI INST OF MATERIA MEDIC) 22 May 1996 (1996-05-22) the whole document	1-27
X	US 5 225 562 A (MCCHESNEY JAMES D ET AL) 6 July 1993 (1993-07-06) the whole document	1-27
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Int. Patent Application No.

PCT/GB 99/02267

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 456 149 A (HOECHST AG) 13 November 1991 (1991-11-13) the whole document ----	1-27
X	EP 0 362 730 A (HOECHST AG) 11 April 1990 (1990-04-11) the whole document ----	1-27
Y	WO 93 08195 A (UNIV SYDNEY) 29 April 1993 (1993-04-29) the whole document ----	1-27
P,X	POSNER, G.H.: "Antimalarial peroxides in the quinghaosu (artesimin) and yingzhaosu families" EXP.OPIN.THER.PATENTS, vol. 8, no. 11, November 1998 (1998-11), pages 1487-1493, XP002119814 LONDON the whole document ----	1-15,20
P,X	WO 99 33461 A (HAUSER INC ;UNIV JOHNS HOPKINS (US)) 8 July 1999 (1999-07-08) the whole document -----	1-27

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Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 26 and 27 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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Patent document cited in search report		Publication date	Patent family member(s)	Publication date
CN 1122806	A	22-05-1996	NONE	
US 5225562	A	06-07-1993	NONE	
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